Chapter 2
The Olfactory Systems

Abstract The 1990s became the decade that olfactory neuroscience showed extraordinary development. Now we have much better understanding of how we distinguish various odors and how the signaling pathways are in the brain. We also know that the olfactory system is not a single system but it is a group of systems in the nasal cavity that respond to chemical compounds. It has been believed for decades that pheromones are received at the vomeronasal organ and the signaling pathway from there reaches to hypothalamus and activates GnRH neurons, however, recent studies have determined that the pathway that reaches to GnRH neurons starts from the main olfactory epithelium. There are pheromones that have receptors in the accessory olfactory system releasing behaviors. The responses to odors/pheromones are not always the same but they change at the sensory neuron level and these changes are regulated by hormones. *It is a chemical signaling process.*

Keywords Main olfactory system · Accessory olfactory system · Olfactory receptors · Signaling pathways · Hormones

2.1 The Olfactory Systems

The most well-known olfactory system is the main olfactory system and the accessory olfactory system (vomeronasal system) (Brennan and Zufall 2006; Spehr et al. 2006) (Fig. 2.1). There are several other systems (Breer et al. 2006; Fleischer et al. 2009), for example Grüneberg ganglion and septal organ (the organ of Masera), which are located in different regions in the nasal cavity. The Grüneberg ganglion is located at the tip of the nose and recent studies have suggested its role in detecting life threatening toxic chemicals or alarm pheromones. The septal organ is located in the central area or middle between the main olfactory system and accessory olfactory system in the nasal cavity. There are some others classified to be different in the type of receptors they carry but located in the main olfactory system area as well, for example, trace amine-associated receptors (TAARs) and

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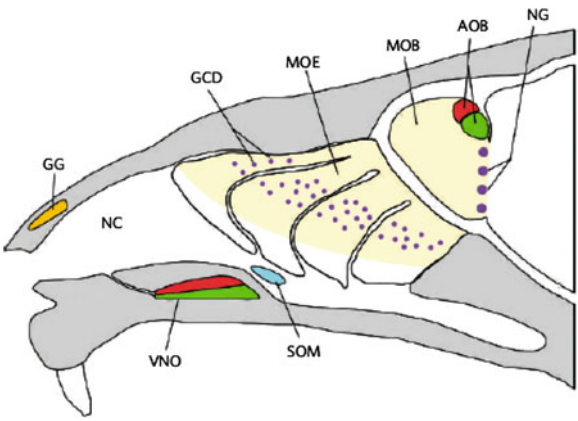

Fig. 2.1 The olfactory system in mice (from Brennan and Zufall 2006). *AOB* accessory olfactory bulb, *GCD* guanylylcyclase type D system, *GG* Grüneberg ganglion, *MOB* main olfactory bulb, *MOE* main olfactory epithelium, *NC* nasal cavity, *NG* necklace glomeruli, *SOM* septal organ of Masera, *VNO* vomeronasal organ

olfactory-specific guanylyl cyclase type D receptor (GC-D). Much is not known yet about the function of olfactory systems other than the main and accessory olfactory system. There are many review articles and books on the olfactory neuroscience that here I will just briefly list and summarize the main and accessory olfactory system.

2.2 The Main Olfactory System and Its Pathway in Relation to Pheromone Signaling

What we usually call "the nose" in humans is precisely saying the main olfactory system. The olfactory epithelium of the main olfactory system is located at the posterior end of the nasal cavity (top of nasal cavity in case of humans) on the surface of cartilage of labyrinth like shape protuberance. Structurally it is composed of olfactory sensory neurons, supporting cells, and basal cells. The olfactory sensory neurons are bipolar neurons with ciliated dendrite, which extend into the mucosal surface and G protein–coupled receptors for the chemical signals are located on these cilia. Olfactory receptor genes started to be identified from early 1990s (Buck and Axel 1991). Over 1000 different types of olfactory receptors are identified in mouse (compared to less than 400 in humans) (Sullivan 2002; Zhang and Firestein 2002; Tirindelli et al. 2009). The axon terminals from olfactory sensory neurons with the same olfactory receptor create a single (or a couple of) glomerulus in the olfactory bulb. Thus, activation of many olfactory sensory neurons with the same olfactory receptor will be converted into an activation of a single glomerulus in the olfactory bulb, which enables the discrimination of odors in the environment. Higher concentration of an odor will activate larger number of olfactory sensory neurons with the receptors for the specific odor and thus stronger

signaling will be conveyed to induce the cognitive outcome of the "notice of strong smell".

In other words, it is possible to say that the main function of the main olfactory system has been traditionally considered to be the detection, discrimination, and recognition of odorants, i.e., involved in cognitive function, whereas, the accessory olfactory system was considered to be an unconscious pathway, detecting pheromones and altering hormone secretion. However, recent studies have shown that the main olfactory system is the one that transfers signals toward gonadotropin releasing hormone (GnRH) neurons, i.e., the neurons that synthesize and secrete gonadotropin releasing hormone (Yoon et al. 2005) (Fig. 2.2). In relation to social contexts, the main olfactory system seems to be involved in mate preference, mate recognition (Baum 2012), and onset of maternal behaviors (Baum and Cherry 2014) and recent studies have shown that pheromones are detected at the main olfactory system as well (Xu et al. 2005; reviewed in Baum and Cherry 2014). It is highly possible that the main olfactory system is involved in inducing primer effects.

These findings on the pathway from main olfactory system to GnRH neurons had strong impact to the studies of species that are known to lack functional accessory olfactory system, like in the higher primates including humans. Studies have been reporting the phenomenon that suggest the existence of pheromonal signaling in these species, although the accessory olfactory system had been found to be residual without functional activity or without axon terminals from the vomeronasal organ reaching to accessory olfactory bulb. Whether the signaling from main olfactory system to the GnRH neurons is causing the primer effects in higher primates is necessary to be clarified hopefully in near future. Conversion of main and accessory pathway was also found in the accessory olfactory system, i.e., some portion of the signaling goes to the main olfactory pathway and reaches to the cortex (Von Campenhausen and Mori 2000; Boehm et al. 2005). This suggests that the accessory olfactory pathway may also not be an "unconscious" pathway. It is maybe more possible that the system used in detecting specific pheromones depends on the characteristics of the pheromones as chemical compounds (for example, chemical structure or molecular weight which is related to volatility) or the adaptive function of the pheromones (in what social context it is related; mating, parenting, affecting reproductive condition, or informing life threatening danger nearby).

The main signaling pathway from the olfactory epithelium reaches to main olfactory bulb (MOB), which then projects to the anterior cortical nucleus of amygdala (ACN), posterolateral cortical amygdaloid nucleus (PLCN), and to the ventrolateral surface of the brain, the anterior olfactory nucleus (AON), the olfactory tubercle (OT), and the olfactory cortex (piriform cortex (Pir), and entorhinal cortex (EC)) (Figs. 2.2 and 2.3). Thus the signaling from the main olfactory bulb projects to hypothalamus and amygdala (Boehm et al. 2005; Yoon et al. 2005; Kang et al. 2009), which suggest that the alterations of hormone secretion can be mediated by the main olfactory system. Studies have shown that, when female mice were exposed to volatile odor of male urine (wind of air blown over urine without direct contact to the urine), immediate early gene Fos was expressed in their

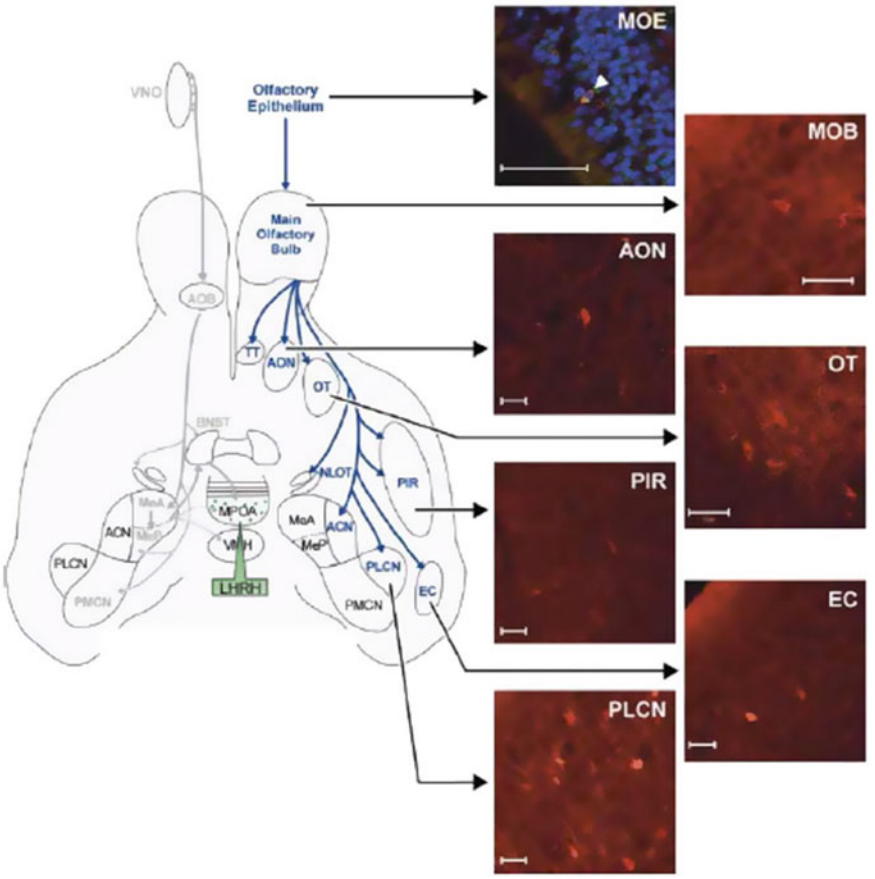

Fig. 2.2 The pathway to GnRH neurons was determined to be the main olfactory pathway (right in *blue*) using infection to Ba2001 virus, which carries *tau-GFP*, infects neurons selectively noninvasively, and spread in a retrograde way from postsynaptic to presynaptic (from Yoon et al. 2005). This was against the common knowledge that the pathway from accessory olfactory system stimulates GnRH neurons. Transgenic mice with CRE recombinase expressed in *GNRH1* (*LHRH*) gene were infected with Ba2001 to let gfp expressed in the GnRH neurons and spread backwards. Photos on the right show immunofluorescence staining against gfp. Scale bars = 50 um. *AON* anterior olfactory nucleus, *EC* entorhinal cortex, *MOB* main olfactory blb, *MOE* main olfactory epithelium, *OT* olfactory tubercle, *PIR* piriform cortex, *PLCN* posterolateral cortical amygdaloid nucleus

amygdala but female urine and cat urine did not make significant changes (Kang et al. 2009), which suggested that the main olfactory system transfers pheromonal information, although it may not be all types of them. However, in other studies using a single type of female pheromone, 2-Heptanone, activation of both main and accessory olfactory bulb of female mice was observed in high-resolution functional magnetic resonance imaging (fMRI) (Xu et al. 2005). In some studies both males

and females showed increased Fos immunoreactivity at the vomeronasal neurons, bulbs, and in the brain, when they were exposed to male-soiled bedding directly (and not to wind containing volatile odor) compared to clean bedding (Halem et al. 1999). These studies suggest that the differences in the influences may depend on the direct/indirect access to the source and also by the way the activation was measured.

2.3 Accessory Olfactory System (Vomeronasal System)

Accessory olfactory system, or the vomeronasal organ, is located in the bottom of the nasal cavity. It is a blind alley hole in the bone with epithelium on one side of the surface of the hole. The amazing mechanical system to bring chemicals into this blind alley is the blood vessel running along the vomeronasal organ. This mechanical system is called vomeronasal pump. The changes in the size opening of the hole caused by the pulsation serve to mechanically pull the chemicals inside the hole from the entrance of vomeronasal organ and to reach to the area where sensory neurons are located. The faster and stronger the heart beats, the more the chemicals will be mechanically pulled into the vomeronasal organ. The sensory neurons, i.e., the vomeronasal neurons, are bipolar neurons like the olfactory sensory neurons but have villi instead of cilia, with receptors on the villi. Axon terminal integrates into glomeruli at the backside of the olfactory bulb (accessory olfactory bulb) and, interestingly, the axons with different receptor types construct a glomerulus (in the main olfactory system, axons with the same receptor type construct a glomerulus). These studies suggest that multiple chemical compounds can induce the same phenomenon by activating different types of vomeronasal neurons and they presumably reach to the same vomeronasal amygdala region in the brain. These hypotheses need to be further tested in future. The signaling pathway was traditionally considered to be the one that reaches to hypothalamus and amygdala and produces changes in the hormone secretion by stimulating GnRH neurons, and thus stimulating the secretion of luteinizing hormone (LH). However, as written above, recent studies have shown that the signaling pathway that reaches to GnRH neurons and thus most likely related to primer effects is the main olfactory system (Yoon et al. 2005). Instead, there are some recent studies showing that pheromones involved in releasing effect are detected by the vomeronasal system (Kimoto et al. 2005; Chamero et al. 2007; Haga et al. 2010; Papes et al. 2010).

Pheromone receptor gene family was first reported in 1995 (Dulac and Axel 1995). So far there are two groups of vomeronasal receptor genes classified, *V1R* and *V2R*, from the type of G protein expressed, i.e., $G_{\alpha i2}$ and $G_{\alpha o}$ (Matsunami and Buck 1997; Buck 2000), respectively, which are both different G protein alpha subunit from those expressed in the main olfactory system (Sullivan 2002). Vomeronasal neurons with V1R receptors are located in the apical layer of the vomeronasal organ and that with V2R receptors are located in its bottom layer. The region in the accessory olfactory bulb that the axon terminals reach is also different.

Those from V1R type vomeronasal neurons reach to the rostral area of the accessory olfactory bulb and those from V2R type vomeronasal neurons reach to its posterior area. From the accessory olfactory bulb, the signaling reaches to four nuclei of the limbic system, the medial (MeA/MeP) and posteromedial amygdaloid cortical nucleus (PMCN), and bed nucleus of the accessory olfactory tract (NAOT) and posteromedial bed nucleus of the stria terminalis (BNST) (Yoon et al. 2005; Dulac and Wagner 2006; Rodriguez and Boehm 2008; Baum and Kelliher 2009) (Fig. 2.3). From these areas, the neurons relay to hypothalamic nuclei (medial preoptic area (MPOA), and ventromedial hypothalamus (VMH), and premammilary and supraoptic nuclei) (Dulac and Wagner 2006). It is known that most of the volatile and semi-volatile pheromones identified to induce or suppress estrus in female mice stimulate V1R neurons and nonvolatile major urinary proteins

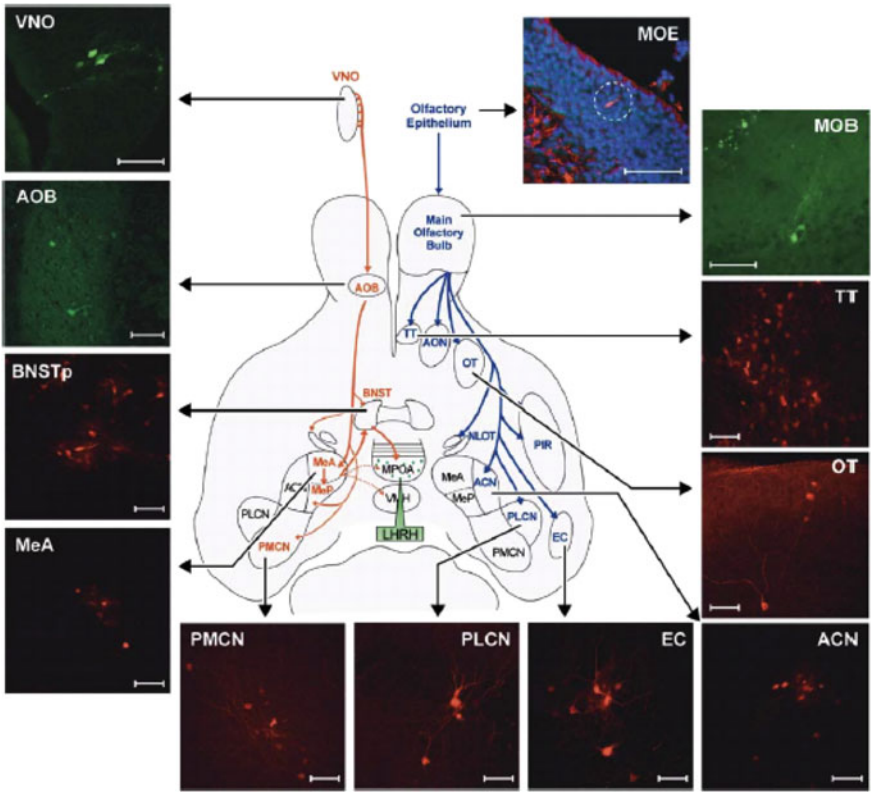

Fig. 2.3 Signaling pathway of the main olfactory system (*right*) and accessory olfactory system (*left*) (from Yoon et al. 2005). *ACN* anterior cortical nucleus of amygdala, *AOB* accessory olfactory bulb, *BNSTp* posterior division of bed nucleus of the stria terminalis, *EC* entorhinal cortex, *MeA* medial amygdaloid nucleus, *MOE* main olfactory epithelium, *MOB* main olfactory bulb, *OT* olfactory tubercle, *PLCN* posterolateral cortical amygdaloid nucleus, *PMCN* posteromedial cortical amygdaloid nucleus, *TT* tenia tecta, *VNO* vomeronasal organ, scale bars = 50 um

(MUP) and MHC class 1 peptides stimulate V2R neurons (see Chap. 3 for the details of these pheromones) (Tirindelli et al. 2009). In addition, MUP is known to have strong affinity with a male murine pheromone 2-sec-butyl-4,5-dihydrothiazole (SBT) (Zidek et al. 1999; Sharrow et al. 2002), which is one of the volatile male pheromone that stimulates V1R (Tirindelli et al. 2009) and induce estrus in adult females (Jemiolo et al. 1986). Binding of SBT with the large nonvolatile MUP delays the loss of function of SBT as a pheromone due to evaporation and dispersion (Hurst and Beynon 2004).

2.4 Responses to Pheromone Are not Always the Same

In the history of studies on olfactory sense, it has been generally considered that olfactory sense is stronger in females and also generally known that people will lose sensitivity to smell by ageing. Changes in the olfactory sense in the same person have been considered to happen also by menstrual cycles but mechanistic details had not been known yet. A new study using mice led by Lisa Stowers has shown recently (Dey et al. 2015) that the sensitivity to detect male pheromone changes in female mice along their estrous cycles, i.e., they become more sensitive during estrous stage and less sensitive during post- and di-estrous stages.

The study first showed that, when female mice were in estrus, they showed preference to one of the two rooms of the test apparatus where there was a male pheromone MUP (see Chap. 4) absorbed in a blotting paper on a wall, but they did not show the preference when they were in di-estrus (Fig. 2.4a). Such differences in the behavior could be explained in a way that they detected the smell of male pheromone but they were ignoring it because they were not in reproductively active state. However, the study showed that the differences were at the sensory system level, and the number of vomeronasal neurons that became activated indicated by calcium influx following exposure to recombinant MUP (rMUP), was significantly higher in the neurons obtained from estrous females than those from di-estrous females (Fig. 2.4b).

As these changes took place along the estrous cycles, Stowers group hypothesized that maybe the sex hormones were involved in modifying the responses. They isolated vomeronasal neurons from ovariectomized mice, added either estrogen or progesterone in the culture buffer, and exposed them to rMUP (Fig. 2.5a). When there was nothing added in the culture buffer, the level of responses to rMUP was not different from the neurons obtained from females in estrus state. When estrogen was added, the level of response was again not different. When progesterone was added at the level of females in estrus, the level of responses was similar, however, when progesterone was added at the high level of progesterone in the females in di-estrous status, the level of responses dropped.

The Stowers group then conducted a thorough investigation of the gene expression in the vomeronasal organ and found that progesterone receptor membrane-component 1 protein (PGRMC1) was expressed. To determine if

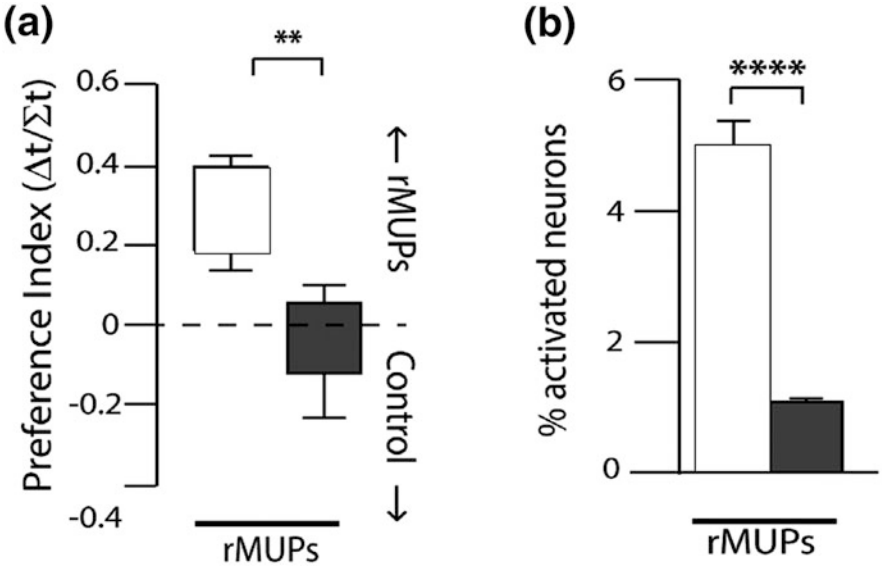

Fig. 2.4 Responses to rMUP (modified from Dey et al. 2015). **a** Preference to the space with the odor of rMUP was high in females in estrus compared to those in di-estrus. **b** Percentage of vomeronasal neurons (VN) activated by exposure to rMUP was high in the VNs from females in estrus than in di-estrus. *Blank bar* estrous female or VN from estrous female, *black bar*: di-estrous females or VN from di-estrous females, $^{**}P < 0.01$. $^{****}P < 0.00001$

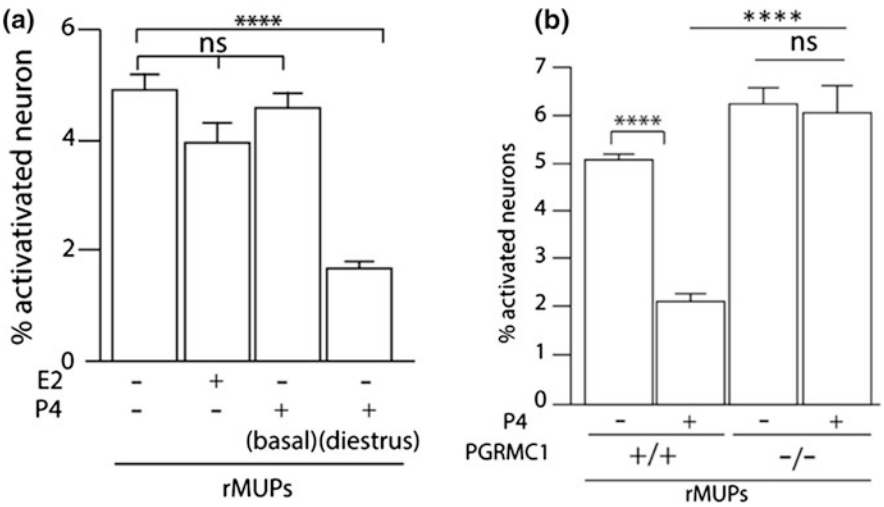

Fig. 2.5 Responses to rMUP in the estrogen or progesterone treated VNs from ovariectomized female mice (modified from Dey et al. 2015). **a** VNs from ovariectomized females treated with estrogen (E2) or treated with progesterone (P4) at basal level or at the level of females in di-estrous stage. **b** VNs from ovariectomized females of transgenic mice that lack progesterone receptors (PGRMC1−/−) or its wild-type (+/+) treated with/without P4 at di-estrous level. $^{****}P < 0.00001$, *ns* not significant

PGRMC1 is involved in the suppression of the responses of vomeronasal neurons to rMUP, they added PGRMC1 antagonist, A205, in the culture buffer for vomeronasal neurons, and then added progesterone at a high concentration as the females in di-estrous status and exposed the neurons to rMUP. They found that the suppressive impact of progesterone was avoided, i.e., it was determined that progesterone is involved in the suppression of the responses of vomeronasal neurons to rMUP at di-estrous status. They also used transgenic mice, which lack PGRMC1 and found that these mice showed preference to the smell of rMUP at any stage of estrous cycle. The vomeronasal neurons from these knockout mice also did not show suppressed responses of activation when they were exposed to rMUP (Fig. 2.5b). These results indicate that the change of responses of the vomeronasal neurons to rMUP is regulated by progesterone and these changes are affecting the preference behaviors to the odor.

Other than the responses to pheromones, recent studies by a group led by Jörg Strotmann of Hohenheim University have also found that the sensitivity of olfaction becomes stronger when mice are hungry (Loch et al. 2015). When we feel hungry, the smell of food always seem to be strong and it is easy to think that it is because you are looking for food and you are thinking of food, i.e., not a change at the sensory system but a change in the cognitive system. However, these studies showed that it was a change in the olfactory system itself and that these changes were regulated by a hormone, ghrelin. Ghrelin was discovered in 1999 as a ligand for a receptor called growth hormone secretagogues (GHS). It is a 28 amino acid peptide that is secreted in the stomach by neuroendocrine cells into the circulation system (Inui et al. 2004). The secretion increases in hunger condition and it is known to be involved in feeding behaviors, memory, and antidepressant effects (Kojima et al. 1999; Sakata and Sakai 2010). The concentration of ghrelin is considered to be high in the hypothalamus but the receptors are activated most at the stomach (Inui et al. 2004). Strotmann group found that ghrelin receptor gene, *ghsr1*, was expressed in the olfactory system. They also tested if ghrelin was secreted locally at the olfactory system or if it reached there through circulating system by testing the gene expression of preproghrelin, which produces ghrelin by posttranslational process of prohormone convertase (PC)1/3 (Walia et al. 2009), and found that ghrelin was not produced locally at the olfactory system. Then they found that, when mice were exposed to odorants (benzaldehyde, 2,3-hexanedione, or 1-heptanal) for one hour after ghrelin (1 uL of ghrelin diluted in water to 1 nM) was applied directly to the nasal epithelium of a mouse, the expression of immediate early gene, *Egr1*, was higher (Loch et al. 2015). Studies using clawed frog (*Xenopus*) larvae also showed that the calcium influx in the olfactory sensory neurons in response to exposure to odorants (mixture of 19 amino acids, which has been known to be food odorants for aquatic animals) was higher when they were kept on hunger condition for 6 h or 12 h than when they were fed ad libitum (Breunig et al. 2010). They also found that one of the endocannabinoids, 2-arachidonoylglycerol (2-AG), and one of the enzymes that is involved in the

synthesis of 2-AG, i.e., diacylglycerol lipase alpha (DAGlα), was expressed more in the olfactory epithelium when the frog larvae is on 6 or 12 h' hunger conditions. When the antagonist to DAGlα, RHC80267, was added to the cultured olfactory epithelium tissue and it was exposed to the food odorant, the calcium influx of the olfactory sensory neurons was suppressed, suggesting the role of 2-AG in the changes of responses. These studies show that the sensitivity of olfactory sense becomes modified, becoming more sensitive in a situation where there are needs in the things that the odor source represents, whether it is food or it is a male to mate, and that, in case of mice, hormone has significant role in regulating the sensitivity.

2.5 Sex Differences in the Responses to Pheromones

The gender differences in the responses to pheromones have been reported in many studies. The most thorough studies have been conducted by collaborative studies by James Cherry and Michael Baum groups of Psychology Department and Biology Department, respectively, both from Boston University. Studies so far have shown that there are sex differences in the immediate gene *c-fos* expression in the vomeronasal organ and medial amygdala when mice were exposed to male-soiled bedding, i.e., females showed more expression than males (Baum 2012). They also showed that the expression of *c-fos* was not different between males and females when they were exposed to the volatile components of urine from males and females (Martel and Baum 2007). The results of these studies suggest that the odor of the same sex may not have impact on vomeronasal pathway but they may have through the main olfactory system.

In our studies on the influences of exposure to synthetic analogs of murine pheromones on cell proliferation in the brain, we found that the exposure to the pheromones of the opposite sex enhanced cell proliferation both in males and females but it did not affect it when mice were exposed to the pheromones of the same sex (Koyama et al. 2013, 2014). However, earlier studies have shown that when female mice were kept in groups their estrous cycles become suppressed (Lee-Boot effect) (Lee and Boot 1955, 1956) and this is caused by the female pheromones (Ma et al. 1998), which is an example that the physiological conditions of females are under the control of the pheromones from the same sex and that indicates that the pheromones of the same sex are detected and processed to cause changes. I have also shown in my early studies that when male mice were housed and established social status, the sperm activity was lower in the subordinate mice (Koyama and Kamimura 1999). Such differences diminished when the vomeronasal organ was removed (Koyama and Kamimura 2003), suggesting that the differences were mediated by pheromones. These studies suggest that pheromones of the same sex do have influences. It is possible that the concentration to affect the same sex need to be higher or also that the reproductive organs are more sensitive than the brain to cause changes.

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